PATHOGENESIS IN VIRAL INFECTIONS

- Viral pathogenesis refers to the processes through which a viral infection leads to disease.
- Viral pathogenesis includes all events that occur in the host from the moment the virus enters the organism until clinical disease develops.
- The outcome of viral infections depends on the complex interaction between viral and host factors.

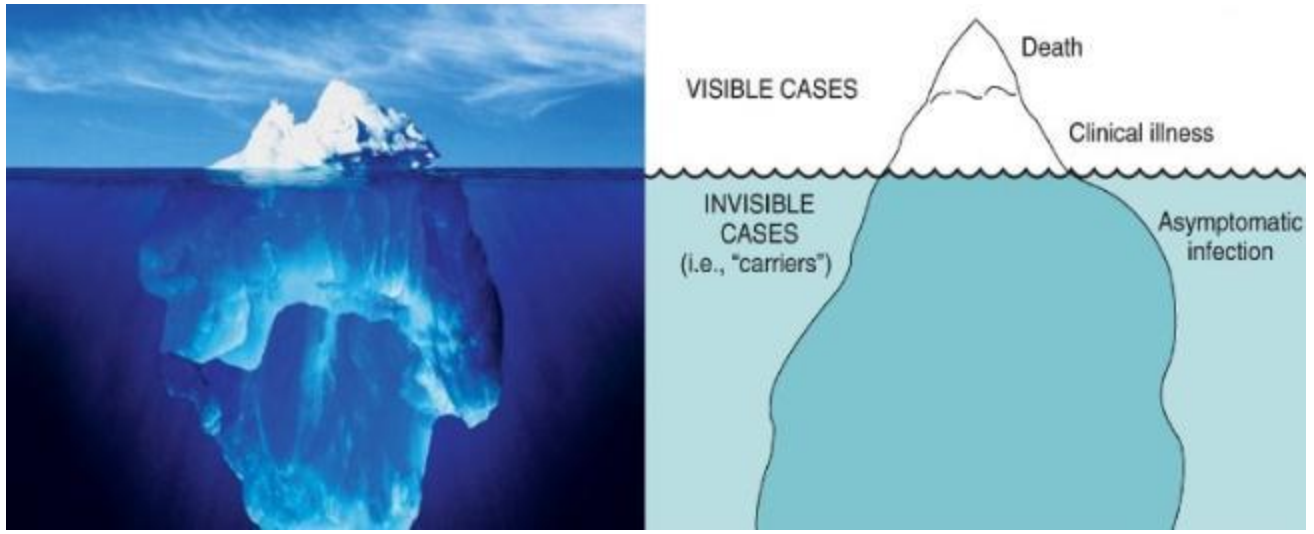
- Viral pathogenesis describes the processes through which viral infections lead to disease. It involves virus–host interactions at cellular and systemic levels that determine disease occurrence, form, and severity.

What's involved?

- How the pathogen enters the organism
- First site of replication
- The way it is disseminated in the organism
- Development of pathological changes and clinical symptoms (disease development)
- Shedding of the pathogen

Heise MT. Viral Pathogenesis. Reference Module in Biomedical Sciences. 2014:B978-0-12-801238-3.00079-9. doi: 10.1016/B978-0-12-801238-3.00079-9. Epub 2014 Nov 28. PMCID: PMC7157475.

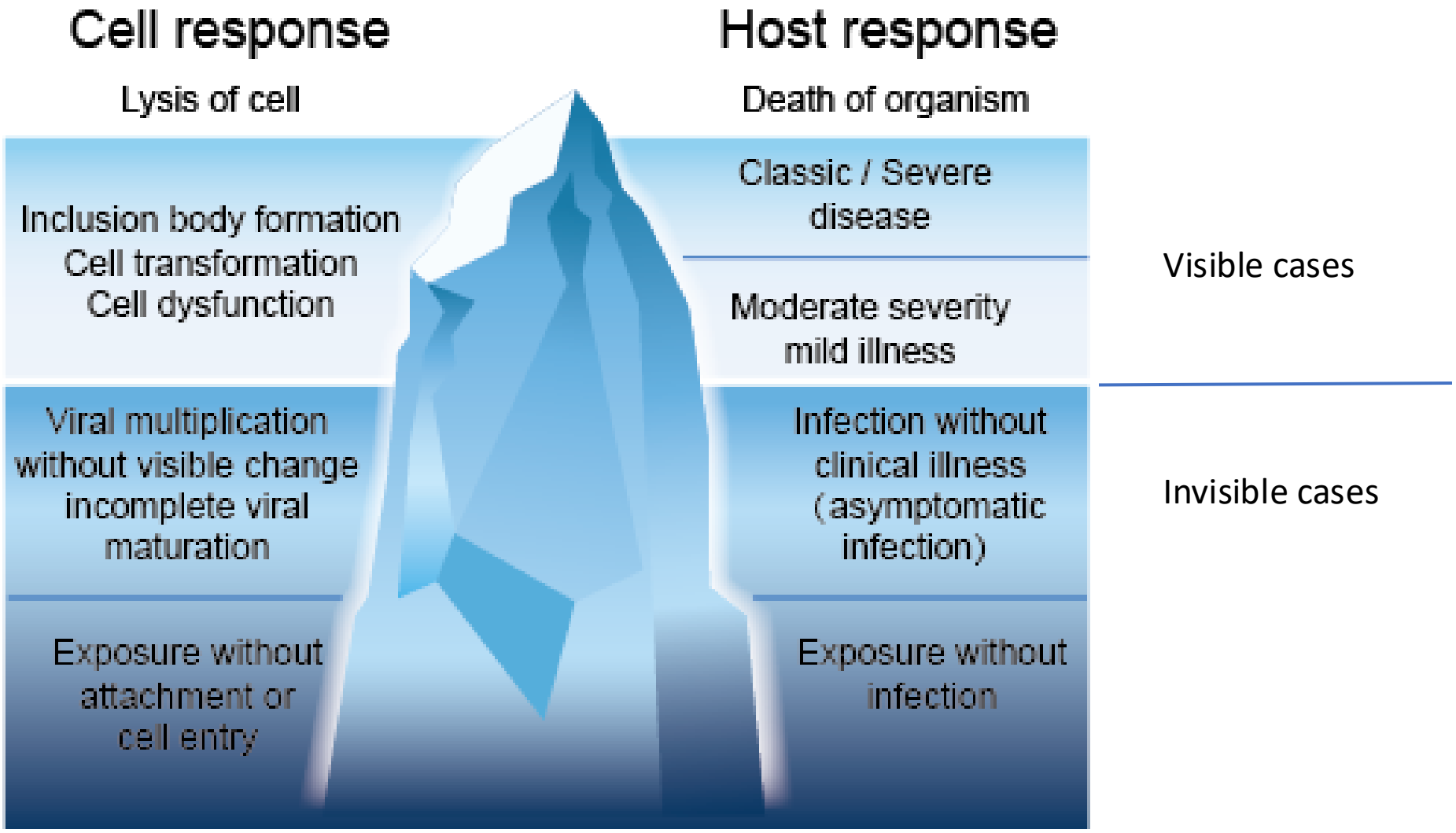
Iceberg concept of infection



- Not every disease is caused by an infectious agent and not every infection may have symptoms.
- Infection is necessarily caused by an agent (such as virus, bacteria, parasite).
- Disease can be defined as a condition that disrupts normal structure or function in the body at the local or systemic level.
    - The majority of interactions with virus do not result in infection.
        - Most infections are asymptomatic or sub-clinical.
    - Infections that cause mild symptoms may not be recognized.
        - Moderate symptoms may be classified as a disease.
    - Only severe symptoms are clearly recognized as a disease.

https://www.docplexus.com/posts/iceberg-phenomenon-of-disease

Eccles, Ronald. (2002). Acute Cooling of the Body Surface and the Common Cold. Rhinology. 40. 109-14.



Iceberg concept of viral infection

https://www.creative-diagnostics.com/Viral-Antigens.htm

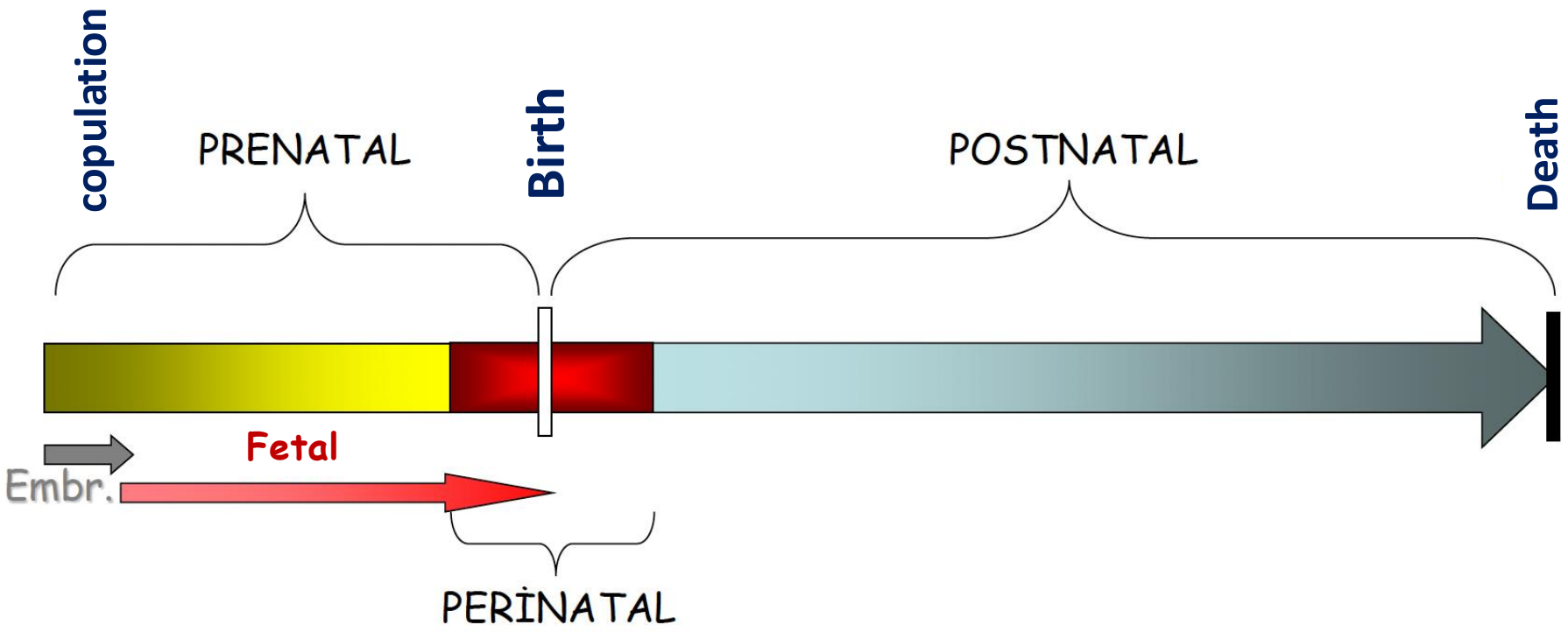
Several factors, both viral and host-related, play an important role in the development of disease. These factors can be summarised as follows:

- For disease to occur, a virus with sufficient quantity and virulence (the ability of the microorganism to cause disease) must enter the host. Viruses that do not have sufficient quantity or virulence cannot cause disease because they cannot overcome the host's defence mechanisms.
- If cells expressing the appropriate receptors are present at the site of entry, viruses can infect by attaching to these cells. Otherwise, they are rapidly eliminated.
- Viruses may fail to cause disease when they enter the host through routes other than their natural route of entry.
    - For example, influenzaviruses cause infection when they enter through the respiratory tract but do not cause disease when introduced directly into the bloodstream.

- If f the host has previously been exposed to a virus and has developed antibodies against it, it may become resistant to infection by the same virus. In such cases, specific antibodies neutralize the virus and prevent infection.
- Various genetic factors affect the development of virus infections.
  - For example, some cat breeds are more susceptible to FIP infection. The factor that is effective in this is the difference of Major Histocompatibility (MHC) genes.
- Nutrition is very important in the development of viral infections. Good nutrition directly contributes to the strengthening of the immune system.
- The health status of the host plays an important role in the course of viral infections. Immunosuppressed individuals are more susceptible to infections, and the incidence and severity of disease are markedly increased in these hosts.

Periods of Exposure to an Infection

1. PRENATAL PERIOD (BEFORE BIRTH)
2. PERINATAL PERIOD (DURING BIRTH)
3. POSTNATAL PERIOD (AFTER BIRTH)



1. Prenatal Period Infections

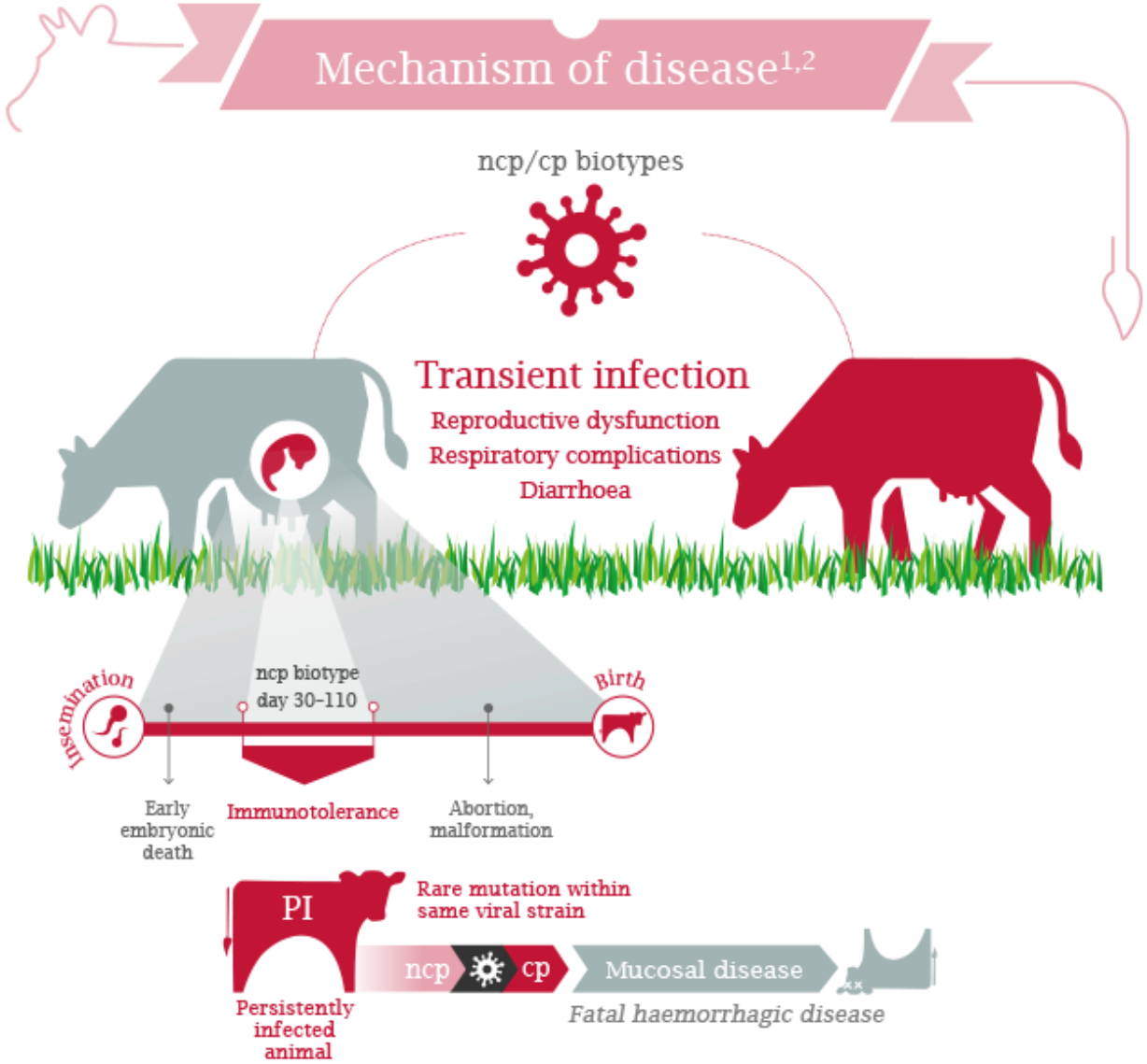
A. During fertilization (via germ cells)

- Infected cells or virus particles may adhere to the zona pellucida of the oocyte or to sperm cells.
  - For example, BVD virus with oocyte or IBR virus (BHV-1) with spermatozoon causes infection in this way.

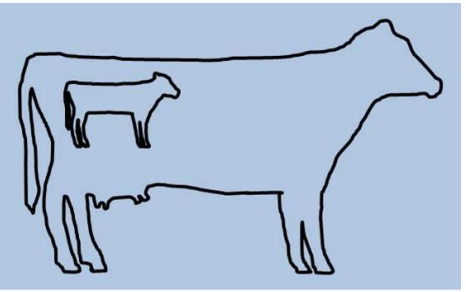
B. When maternal infections are transmitted to the embryo or fetus during pregnancy

1. In utero (infection of the uterine mucosa or uterine wall) BHV-1
2. Transplacental (transmission through the placenta during maternal viremia) Bluetongue, Akkbane, BVDV

B. Example of transplacental (transmission through the placenta during maternal viremia) BVDV infection



How old is the calf foetus?



Months of pregnancy

0	1	2	3	4	5	6	7	8	9

Early embryonic death

Foetal death, the mother could abort

The calf could be born **Persistently infected**

The calf could be born with congenital defects

The calf will be born sero-positive, producing antibody to BVD and **not** persistently infected

https://www.pngegg.com/en/png-opuns
https://www.farmhealthonline.com/disease-management/cattle-diseases/bovine-viral-diarrhoea/

2. Perinatal Period Infections

- Infections occurring after entry of the virus through the birth canal

These infections occur when the virus is transmitted to the newborn during delivery through the birth canal.

1.Maternal Transmission

- Transmission through maternal urine and feces (e.g., CMV, BRV)
- Reactivation of latent infections (e.g., herpesviruses)

2.Iatrogenic Transmission

- Transmission resulting from the use of contaminated materials or medical instruments

3. Postnatal Period Infections

- Direct contact → Canine Distemper Virus
- Inhalation (Aerosol) → IBR, Parainfluenza-3, Pox
- Oral → Rotavirus, Enterovirus, BSE
- Conjunctival → Herpesviruses
- Urogenital → Papillomaviruses, HIV
- Vectors → Bluetongue virus, Akabane, West nile virus
- Bite → Rabies, FeLV, FIV
- Cutaneous → Herpes Simplex Virus (HSV), Vaccinia Virus
- Genital → IBR
- Transfusion → Hepatitis B, Hepatitis C viruses, HIV

- For a virus to cause disease, after entering the body through various routes, it must spread to the target organs following primary replication.
  - **Primary Replication–**refers to the initial site where the virus replicates after entering the host.
- Based on the spread of the virus after primary replication, viral infections can be divided into two groups:

I. They can cause infection locally at the site of entry.

- The virus replicates in tissues near the site of entry into the body. Local infection may occur with primary replication.The virus may then be shed into the environment through feces, body fluids, or respiratory secretions, allowing transmission to susceptible hosts.
  - For example, rotavirus infection.

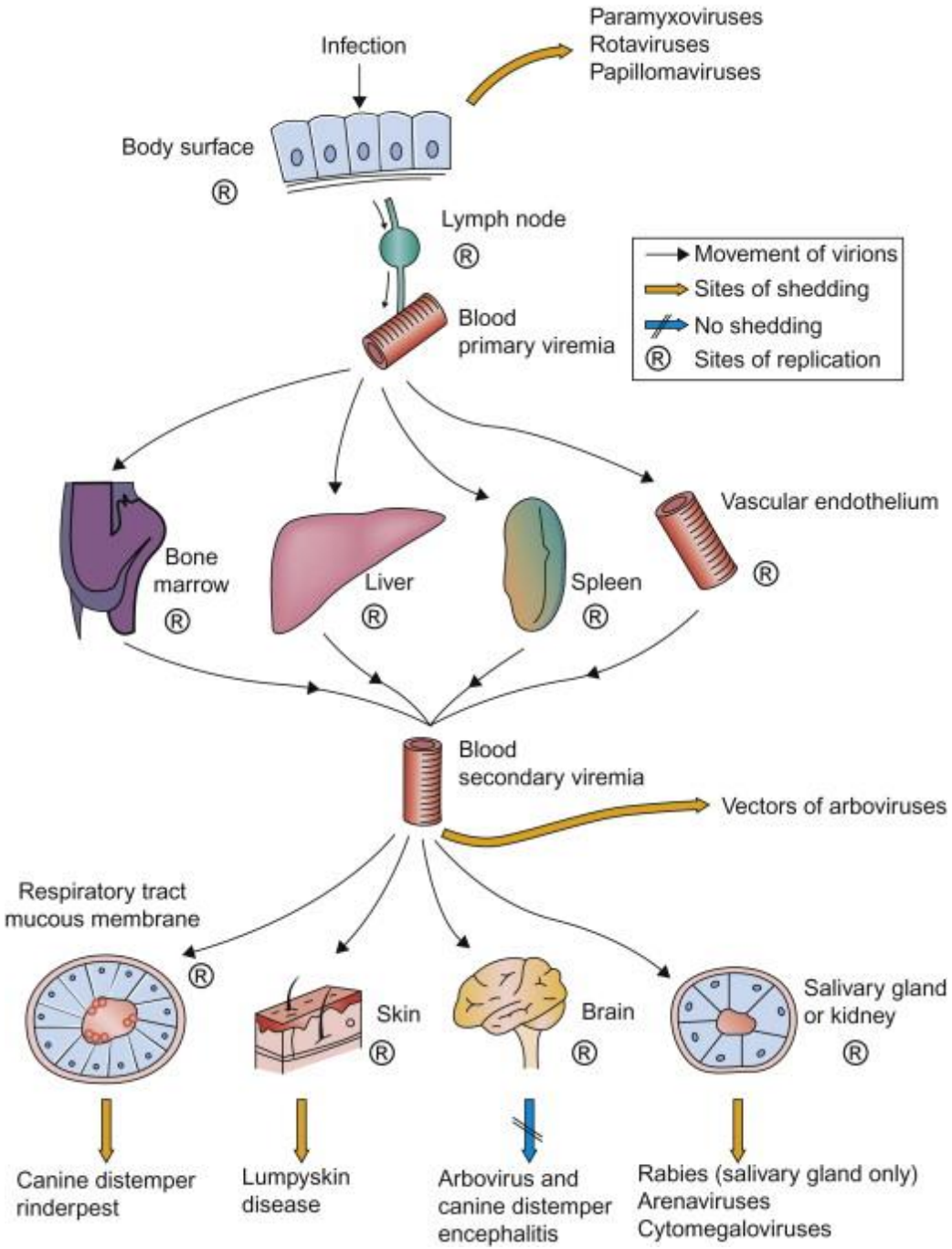
II. Systemic spread.

- For systemic infection to occur, the virus must cross the mucosal barrier and spread to more distant parts of the body. To achieve this, viruses may use the bloodstream, lymphatic circulation, or peripheral nerves to reach their target organs or tissues.
- The virus then infects specific cells in these organs or tissues according to its tissue tropism.

- Systemic spread in viral infections:

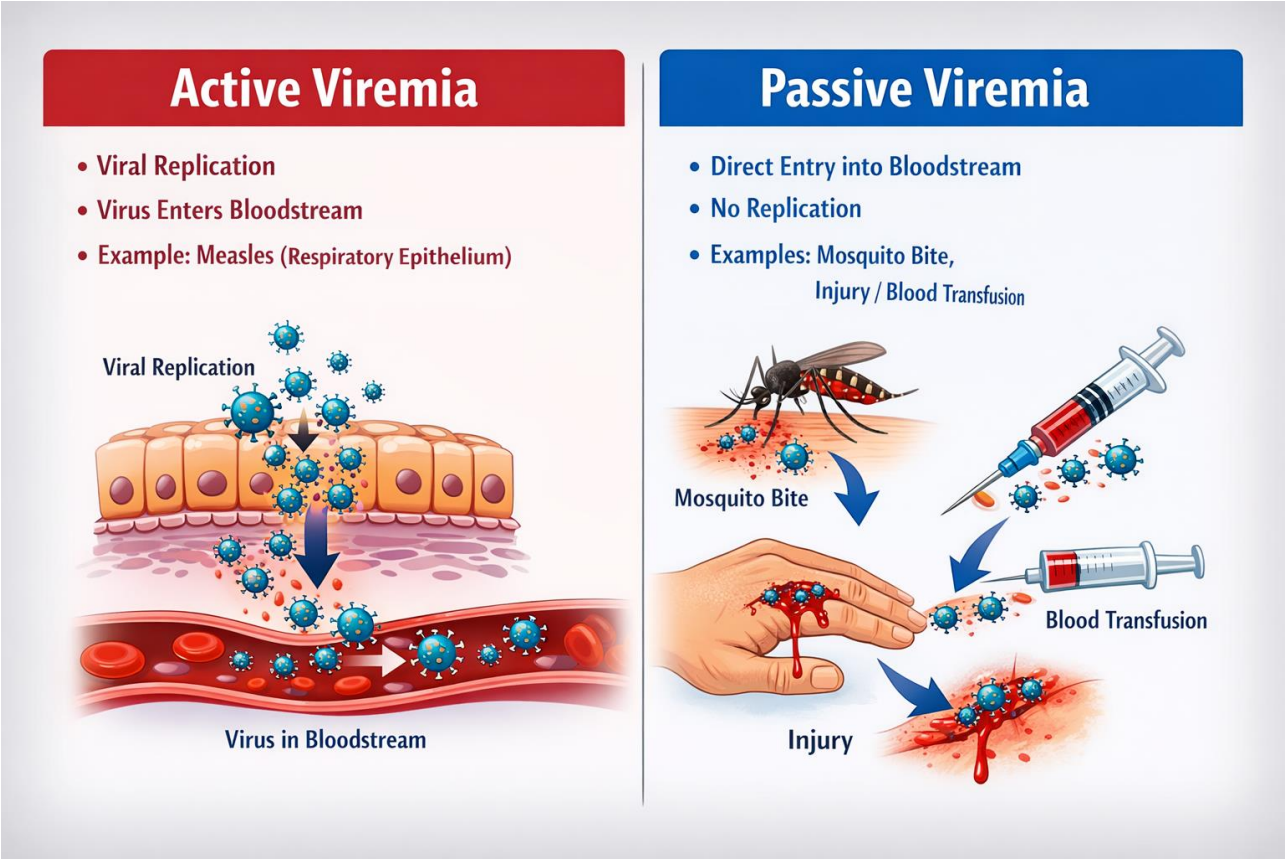
➢ Viremia (spread through the bloodstream)

- At this stage, viruses enter the bloodstream after primary replication and are transported to target organs or tissues according to their tissue tropism.
- The most prominent symptom is fever. In some viral infections, viremia may occur in two phases (biphasic viremia) ---> poxvirus infections.



Pathogenesis of Viral Infections and Diseases, Editor(s): N. James MacLachlan, Edward J. Dubovi, Fenner's Veterinary Virology (Fourth Edition), Academic Press, 2011, Pages 43-74, https://doi.org/10.1016/B978-0-12-375158-4.00003-1.

- Active viremia is caused by the replication of viruses which results in viruses being introduced into the bloodstream.
  - Examples include the measles, in which primary viremia occurs in the epithelial lining of the respiratory tract before replicating and budding out of the cell basal layer (viral shedding), resulting in viruses budding into capillaries and blood vessels.
- Passive viremia is the introduction of viruses in the bloodstream without the need of active viral replication.
  - Examples include direct inoculation from mosquitoes, through physical breaches or via blood transfusions.



➢It is through the nerve pathway. Rabies

Pathogenesis of Rabies

Virus transmitted from saliva to muscle

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Virus travels from neuromuscular junction to peripheral nerves

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From PNS to CNS

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Infects brain, salivary gland

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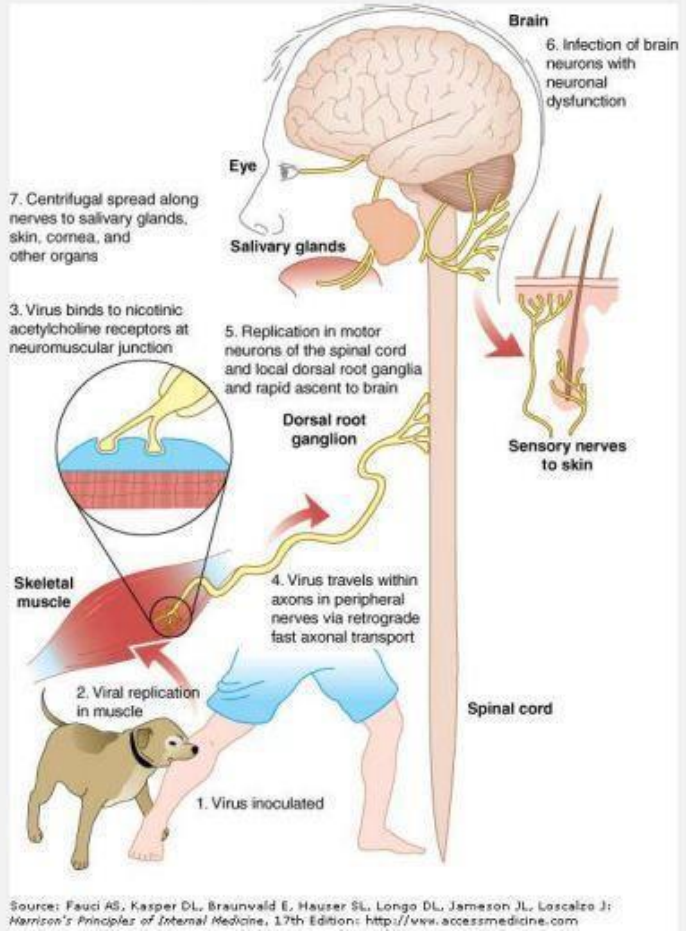
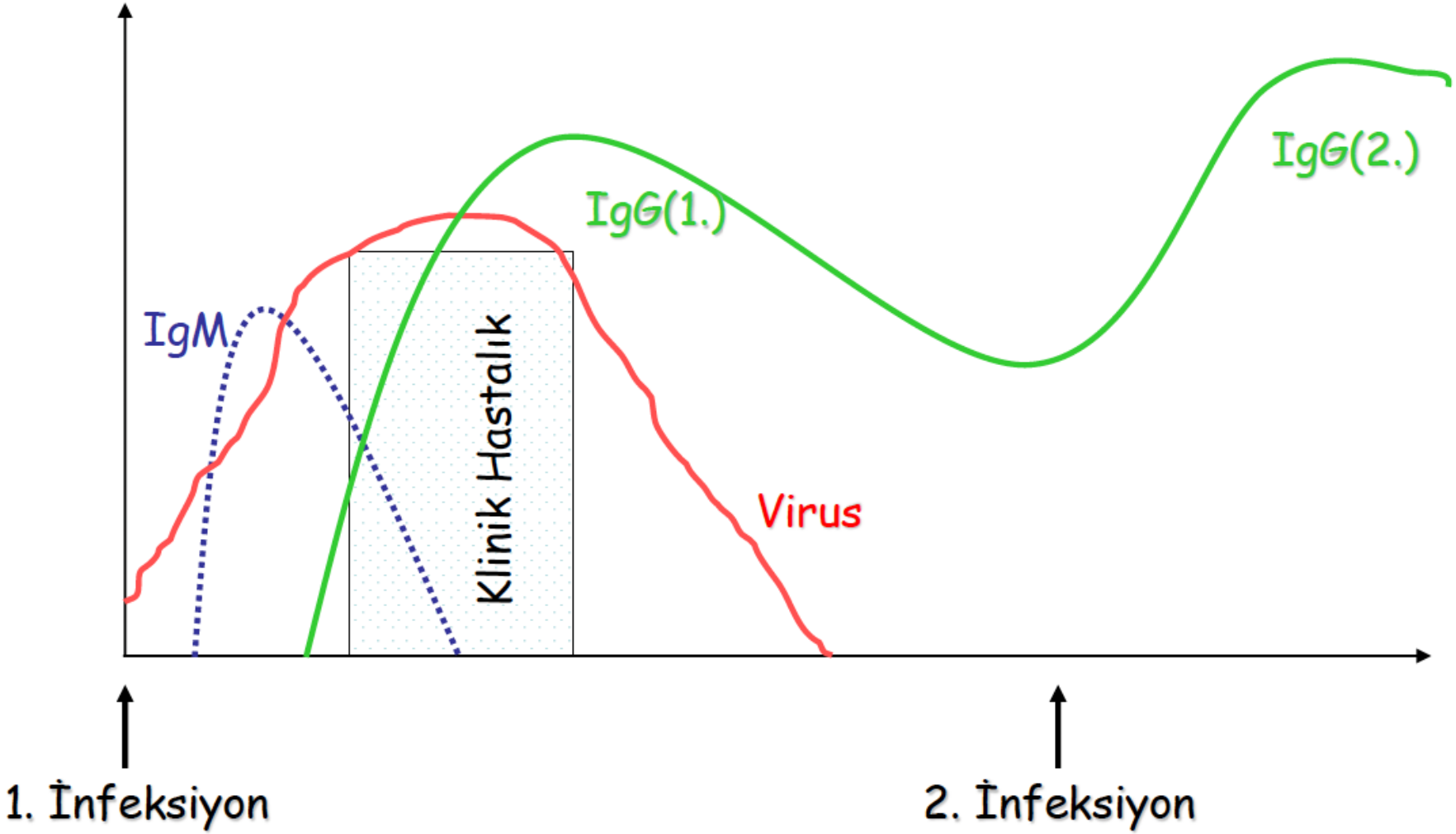
Infects other organs – respiratory tract



Different types of Viral infections

- Depending on their progression; postnatal infections may be acute or persistent
- Acute infection: It is characterized by the development of disease the virus enters the host, followed by elimination of the virus through the host immune response. Acute infections are typically short in duration and followed by rapid recovery.
- Persistent infection: This is a slowly progressive form of infection characterized by a long interval between the entry of the virus into the host and the onset of disease symptoms.
- This may be due to deficiencies in the host immune system, the ability of the virus to escape of the immune response or, in some cases, low virulence of the virus.
    1. Chronic Infections
    2. Slow Infections
    3. Latent Infections
    4. immunotolerant infection

Acute infection:



Persistent Infections

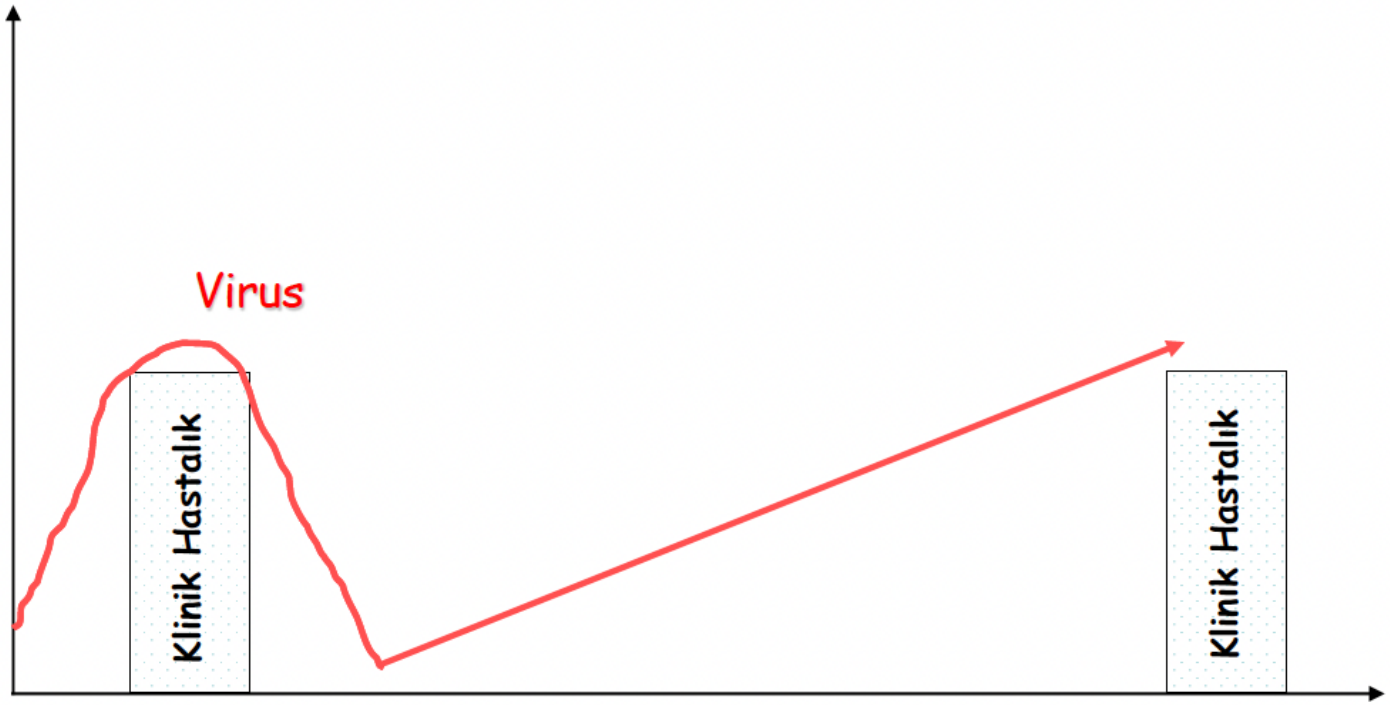
1. Chronic Infections (Old Dog Encephalitis)
2. Slow Infections (Retroviral infections; Caprine Arthritis Encephalitis, Maedi-Visna, AIDS, etc.); Prion infections.
3. Latent Infections (All Herpesvirus infections)
4. Immunotolerant infection (BVDV)

1. Chronic Infections

Old Dog Encephalitis, a late complication of canine distemper, is a good example.

In chronic infections, the virus is not completely eliminated after the primary infection and persists in the host for prolonged periods, often replicating at low levels.

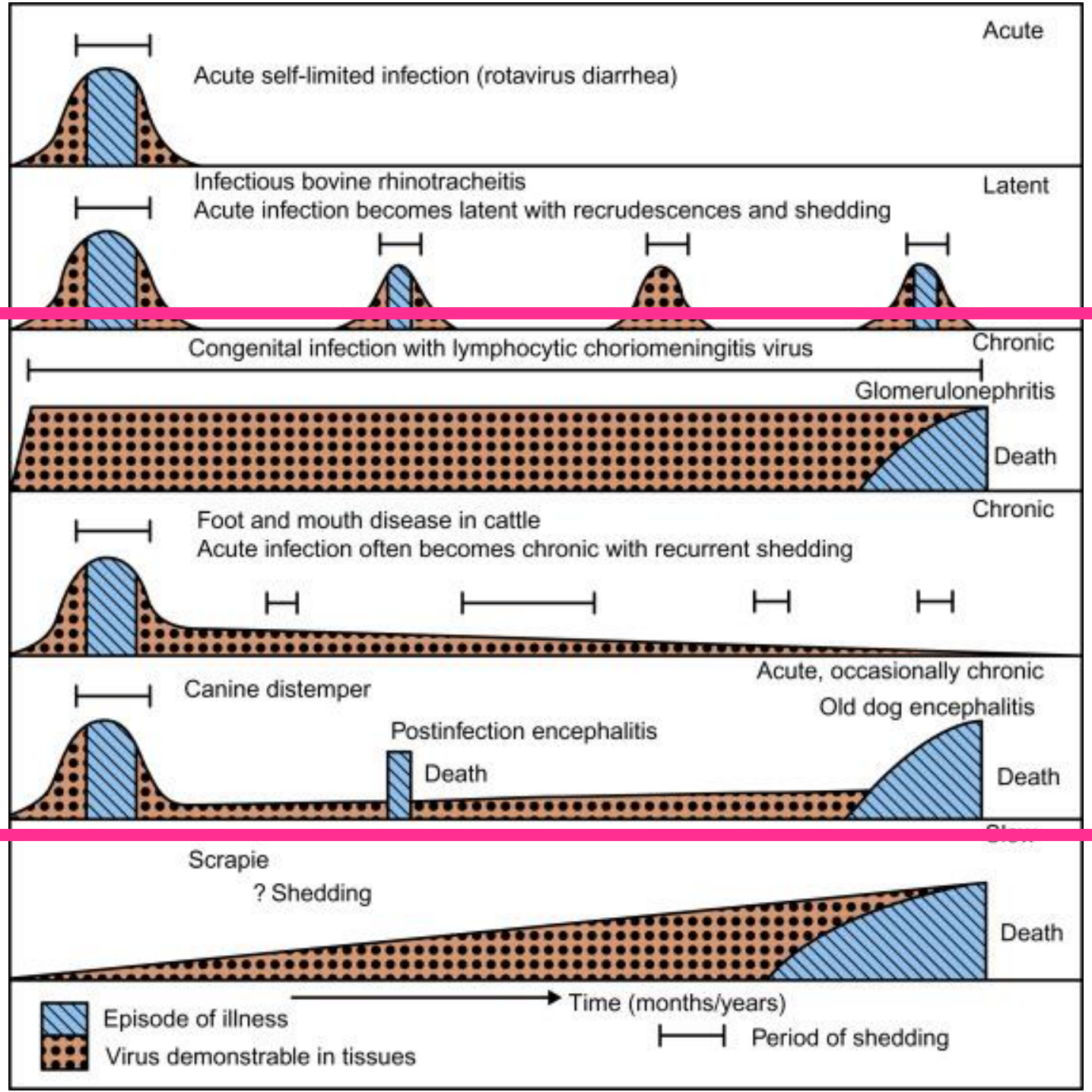
Although the infection tends to regress, late symptoms of acute infection may occur.



Three different course patterns have been identified for this infection model.

These are the chronic form of

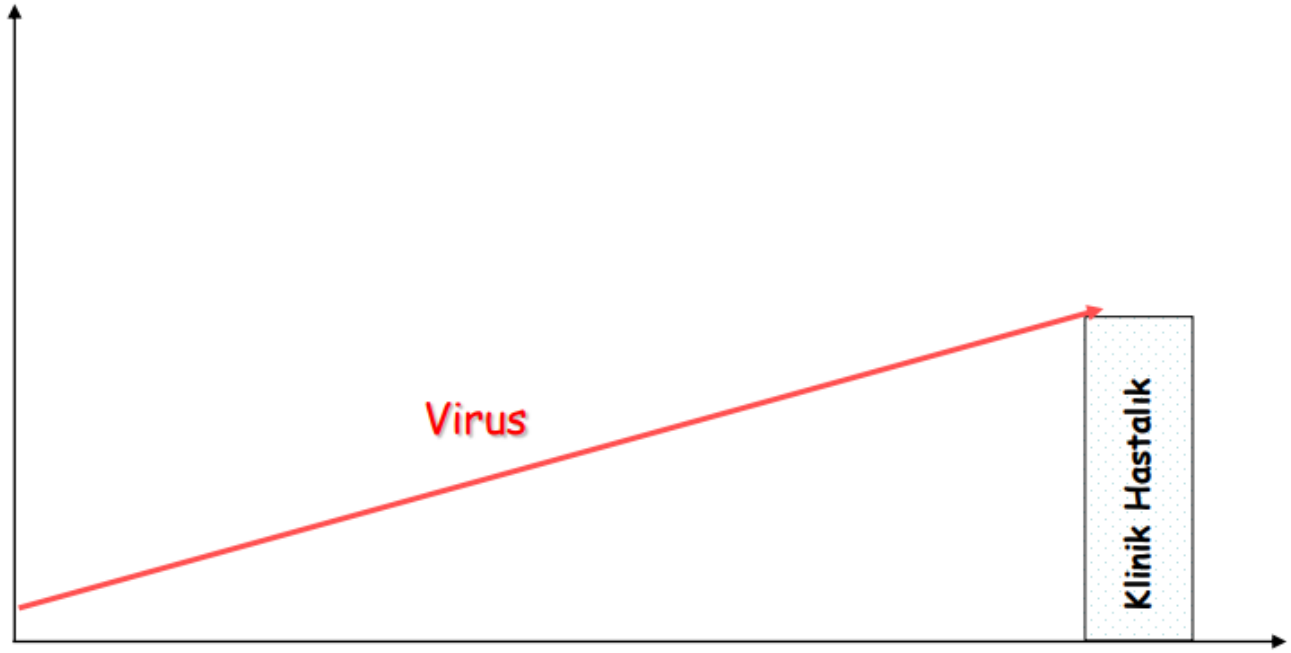
- foot-and-mouth disease,
- the old dog encephalitis form of canine distemper,
- the congenital infection form of lymphocytic choriomeningitis virus.



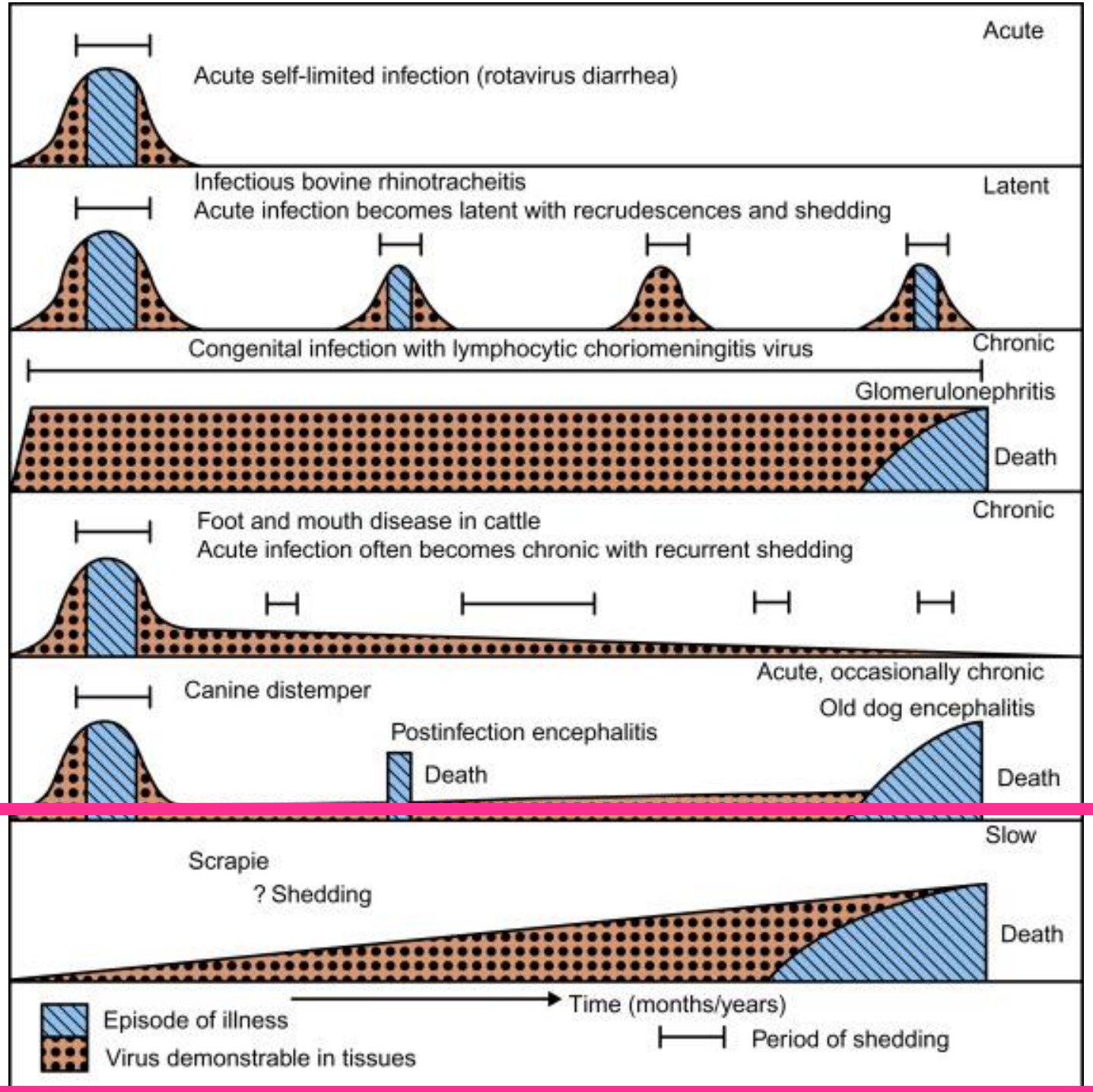
Fenner'sVeterinaryVirology.DOI:http://dx.doi.org/10.1016/B978-0-12-800946-8.00003-9

2. Slow Infections

All retrovirus infections and prion diseases are the best examples of this type of persistent infections.
In these infections, there is a long infection period that progresses very slowly.
During the preclinical period, which can vary from a few months to a few years, the amount of the virus detected in the tissues tends to constantly increase.
In the final stage, disease symptoms appear and these progressive findings result in death.



- Diseases caused by prions (cattle spongiform encephalopathy (BSE), sheep scrapie disease, etc.) and maedi-visna caused by lentiviruses, goat arthritis-encephalitis, feline immunodeficiency syndrome (FAIDS), etc. diseases and some other retrovirus infections (e.g. progressive pneumonia of sheep) are included in this group.



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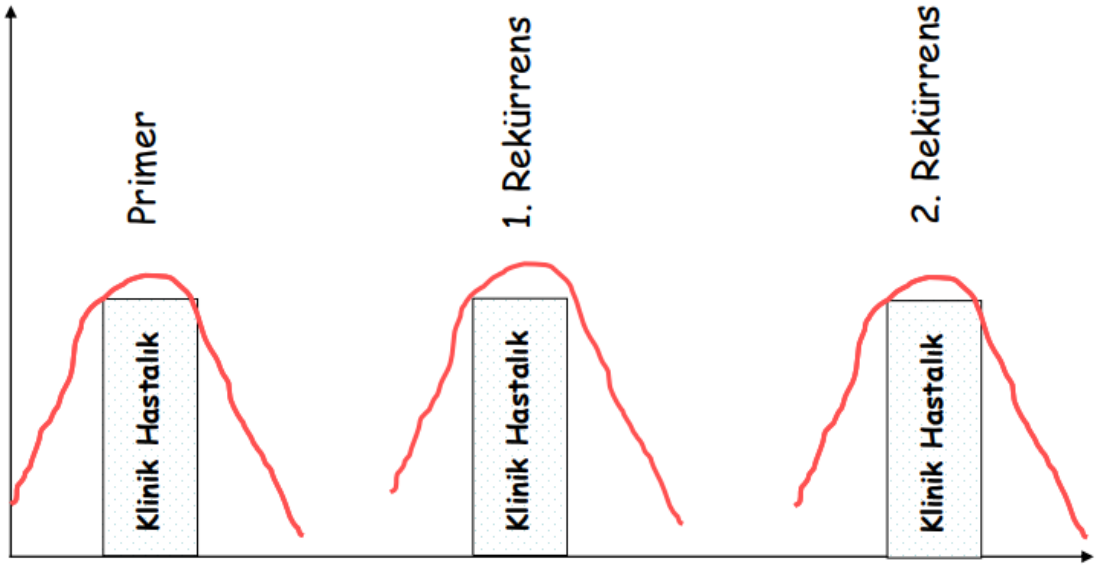
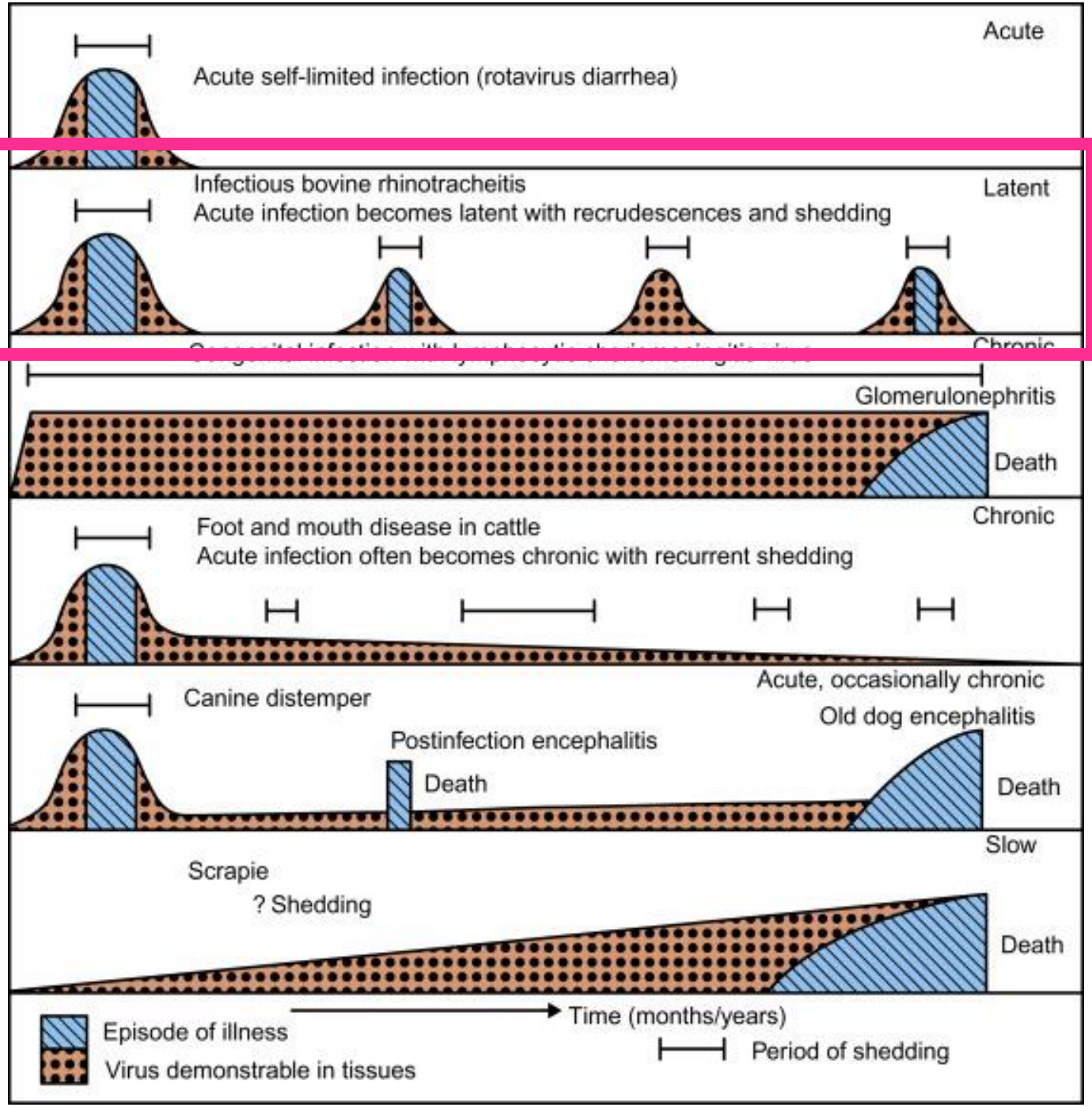
3. Latent Infections

It is characterized by the occasional recurrence of the acute disease.

- Herpesvirus infections are the best example of this. The initial infection is called primary infection, while subsequent episodes are referred to as recurrent infections.
- In the latent infection model, an antibody response develops after the primary infection, and virus-specific antibodies are generally detectable throughout life.
- the most well-known examples of the latent infectior model:
  - Herpes simplex virus infections (HSV-1 and -2) in humans
  - bovine alfaherpesvirus 1 (BHV-1),
  - pseudorabies,
  - equine herpesvirus (EHV-1, EHV-4)
  - feline herpesvirus virus (FHV-1) infections



- Following primary infection, alphaherpesviruses are transported via nerves to the trigeminal or sacral ganglia.
- The viral genome establishes latency in these ganglia and persists in the host for life.
- In later periods, the virus may be reactivated due to stress factors such as pregnancy, transplantation, and corticosteroid treatment.
- Reactivation may occur repeatedly throughout the life of the host.
- During reactivation periods, virus shedding occurs and virus can be detected in tissues or secretions.
- During these episodes, disease symptoms usually reappear, however reactivation may sometimes occur without clinical findings.



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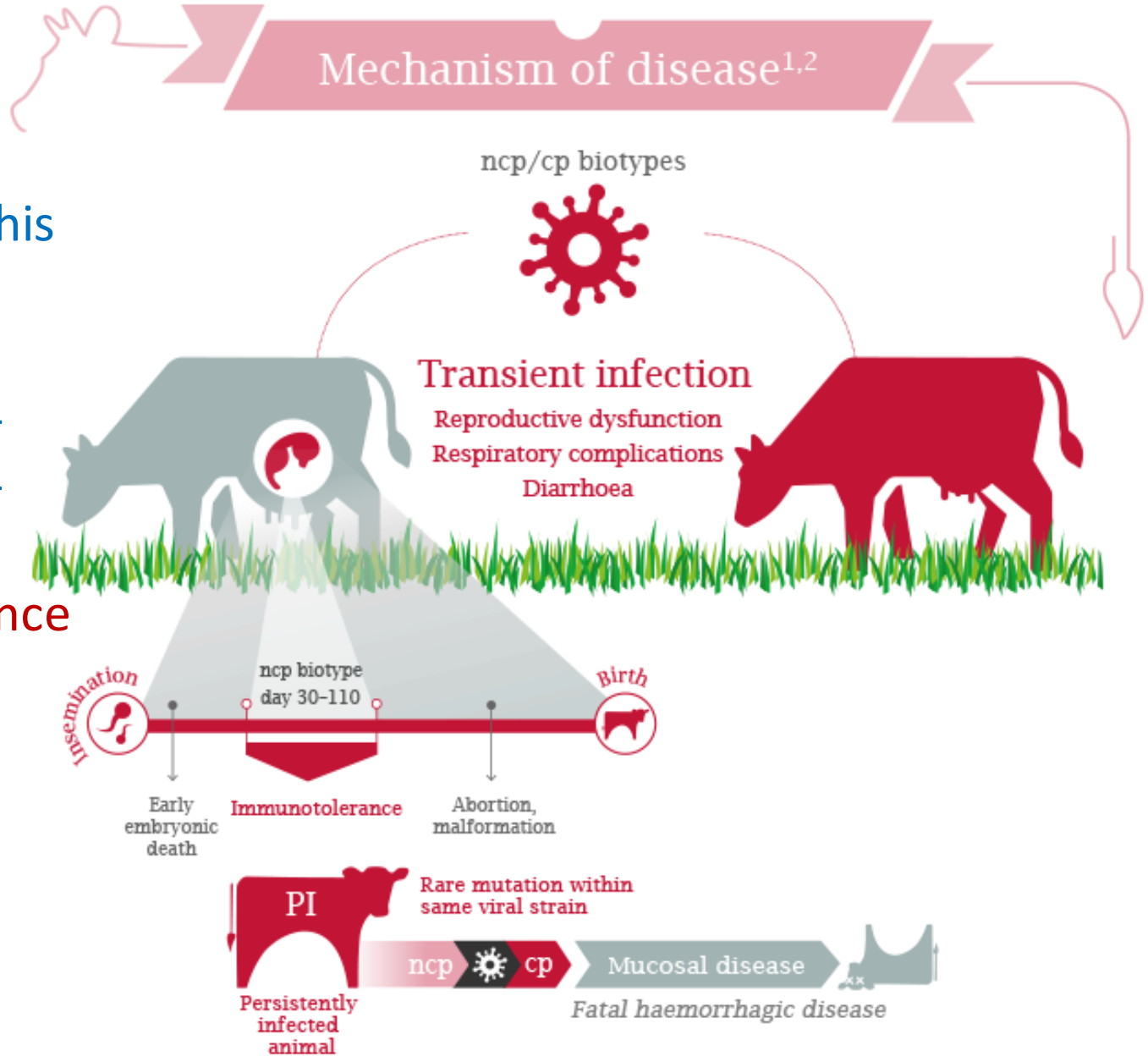
4. Immunotolerant infection

- This infection model observed in **pestiviruses** has a pathogenesis that is completely different from the other three infection models.
- In this model, non-cytopathogenic viral strains infect the fetus in utero before the development an immune response (immunocompetence).
- By the time immunocompetence develops, the virus has already settled in the organism and is recognized as an organismal structure.
- As a result, there is no immunological response against this virus strain and a lifelong **immunotolerance** is formed.
- **Such animals are called persistently infected (PI) animals and play a major role in the epidemiology of pestivirus infections.**
- **PI calves are virus-positive and antibody-negative from birth.**

- There is no immunological response to this virus strain in the host and a lifelong **immunotolerance** develops.
- From the birth, affected calves are virus-positive in virological tests but antibody-negative in serological tests.
- These animals, born with immunotolerance and lifelong persistent infection, are carriers and transmitters of the virus throughout their lives.

Persistently Infected (PI) animals



The Importance of Persistent Infections

1. They may become reactive and exhibit an acute illness pattern at any time. They may cause disease outbreaks again due to reactivation (latent infections).
2. They have epidemiological importance. Since these animals do not show clinical signs, they may silently transmit the virus and contribute to the spread of infection over long distances.
3. They may lead to re-introduction of disease into disease-free/eradicated areas and therefore represent an important challenge in disease control and eradication programs.
4. They maintain the **continuity of infection in nature** and may contribute to virus circulation even in vaccinated animals or herds.
5. Due to **immune suppression**, affected animals may become more susceptible to secondary infections and may contribute to the development of **immunopathological disease complexes**.
6. In some viral infections, persistent infection may also lead to **tumor development**.